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Intensity-Modulated Radiotherapy for Lung Cancer: Current Status and Future Developments

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Abstract: Radiotherapy plays an important role in the management of lung cancer, with over 50% of patients receiving this modality at some point during their treatment. Intensity-modulated radiotherapy (IMRT) is a technique that adds fluence modulation to beam shaping, which improves radiotherapy dose conformity around the tumor and spares surrounding normal structures. Treatment with IMRT is becoming more widely available for the treatment of lung cancer, despite the paucity of high level evidence supporting the routine use of this more resource intense and complex technique. In this review article, we have summarized data from planning and clinical studies, discussed challenges in implementing IMRT, and made recommendations on the minimum requirements for safe delivery of IMRT.

Key Words: Radiotherapy, Lung cancer, Intensity-modulated radiotherapy, Non–small-cell lung cancer, Dose escalation.

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Radiotherapy plays an important role in the management of lung cancer, with over 50% of all lung cancer patients receiving this modality at some point during their treatment. In the radical setting, the ultimate aim of radiotherapy is to achieve local tumor control while limiting damage to the surrounding normal tissue. The impact of local control in non–small-cell lung cancer (NSCLC) has been highlighted by studies demonstrating that it correlates to a survival benefit.[1,2]

In the 1980s, the advent of computed tomography (CT) and the multileaf collimator (MLC) enabled radiation oncologists to shape fields around a target volume with three-dimensional conformal radiotherapy (3DCRT) and this remains the standard procedure in lung radiotherapy.[3] However, despite advances in planning and verification, local progression-free survival and overall survival (OS) rates in locally advanced NSCLC remain low (30% and 10–15% at 5 years, respectively).[1,2,4]

Currently, the standard dose/fractionation for patients with stage III NSCLC is 60 Gy equivalent dose in 2 Gy/fraction (EQD2). One potential reason for low progression-free survival and OS rates in this group may be that this radiotherapy dose is perhaps too low to achieve local control. Martel et al.[5] estimated that doses of 84 Gy in EQD2 are required for 50% probability of tumor control at 3 years, and biologically effective doses in excess of 100 Gy were needed to achieve greater than 90% local control in stereotactic ablative radiotherapy (SABR) studies.[6] These data suggest that higher biologically effective doses may be required to achieve better local control, but evidence to support dose escalation using conventional fractionation is lacking in the current literature.[7] Despite this, many still believe that dose escalation in NSCLC could be of benefit, if facilitated by an improvement in radiotherapy-delivery techniques.

Intensity-modulated radiotherapy (IMRT) is an advanced form of 3DCRT that modifies the intensity of the radiation across each beam in complex ways, sculpting the high-dose volume around the site of disease and thereby sparing adjacent organs at risk. The superior dose conformity that can be achieved allows avoidance of the surrounding normal tissues.[8–14] This technique allows the treatment of radiotherapy volumes previously considered too large for a radical dose and permits safer dose escalation to the tumor (potentially improving local control).

IMRT is currently being used routinely for the treatment of both early stage and locally advanced NSCLC in many international academic centers. However, there are no published randomized trials comparing 3DCRT to IMRT in NSCLC[15] and such studies are unlikely to be forthcoming. In the wider community, uptake of IMRT for lung cancer has been slow, which may in part be due to the relative lack of evidence in this field compared to head and neck and prostate cancer.[16–19] Routine use of this technology also impacts on planning and treatment delivery times, and creates a need for equipment capable of facilitating image-guided treatment. Other considerations include how the "low-dose bath" created by the increased number of beam angles affect acute and late toxicity to the lung[20] and second malignancy risk,[21] and whether improved conformality to the target volume may in fact under-treat micrometastatic disease and lymph node stations previously incidentally treated to a therapeutic dose with 3DCRT.[22]

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In this article, we aim to give an overview of the rationale for IMRT in lung cancer, to present current evidence supporting the use of this technique and finally to highlight future directions.

MATERIALS AND METHODS

This article is a review of the literature rather than a systematic review.

PubMed (1950–2014), EMBASE (1974–2014), and the Cochrane library were searched for phase I–III clinical trials, case-series studies, cohort studies, meta-analysis, and reviews in the English language using the following keywords: lung cancer, NSCLC, radiotherapy, radiation therapy, IMRT, and dose escalation.

Out of initial 118 articles identified by the search terms, 46 were deemed eligible after screening by title and abstract review. In addition, relevant publications and conference abstracts known to the authors were also included.

What is IMRT?

IMRT adds fluence modulation to beam shaping,[23–25] which improves dose conformity around the tumor and spares surrounding normal structures.[23,26] There are two main approaches to static IMRT and both deliver radiation from a number of fixed gantry angles and achieve fluence modulation with different MLC arrangements. In its simplest form each IMRT field is segmented into a number of shaped subfields (step and shoot approach). More complex sliding window techniques move the MLCs during "beam on" time. A further development is rotational IMRT or so-called volumetric-modulated arc therapy (VMAT), whereby the linear accelerator rotates around the patient, continually delivering radiation. As the MLCs change during this rotation, hundreds of fields are generated to create a more conformal dose distribution.[27] Tomotherapy represents another IMRT delivery technique,[28] where dose is delivered using a technology similar to CT (slice-by-slice of helical dose delivery) combined with a binary MLC for fluency modulation.

3DCRT planning typically involves trialing different combinations of beam shapes, weights, and gantry angles until a satisfactory dose distribution is achieved (forward planning). This method is impractical for IMRT, due to the large numbers of fields requiring several MLC arrangements. Therefore, IMRT planning utilizes computerized inverse planning, whereby the desired dose distribution is described by a series of instructions to a computer system, which then uses a cost function to optimize beam shapes, beam fluences, and beam weights to achieve the desired outcome. Advantages and disadvantages of using IMRT for lung cancer are presented in Table 1.

Dose Distributions with IMRT Compared to Conventional 3DCRT

A number of planning studies comparing dosimetric plan quality of 3DCRT and different IMRT techniques have been published in the field of lung cancer. These are summarized in Table 2. All authors except McGrath et al.[29] demonstrate improved planning target volume (PTV) coverage with IMRT.[8–14,30,31] Conversely, the literature reports mixed results with regards to doses to organs at risk. In general, IMRT reduces the volume of whole lung receiving more than 20 Gy (V20),[9–12,29–31] but the effect of IMRT on lower doses to the lung are not as clear; two groups report a reduction of V5[29,31], while another three groups report an increase.[8,10,11] Of the groups who investigated the dose to the heart, four demonstrated an advantage with IMRT[8–10,12] and two did not find any benefit. When spinal cord dose was examined, five out of six groups found a significant advantage with IMRT.[8,10,13,14,30]

Table 3 compares different IMRT planning techniques. Apart from treatment time, there is no clear benefit for one technique above the others. All groups comparing standard IMRT techniques with VMAT found a treatment time advantage in favor of VMAT.[10,14,32–35] For example, Ong et al.[13] showed an 8-minute time reduction if VMAT was used compared to IMRT. Weyh et al.[35] compared tomotherapy, IMRT, and VMAT and reported a significant treatment time benefit using VMAT (6.5 minutes) compared to the other two techniques (IMRT: 11.1 minutes, tomotherapy: 15.9 minutes). The clinical relevance of this, especially for SABR patients, is that treatment slots can be reduced from 30–40 minutes to significantly shorter times.[36,37] This shorter treatment time reduces the risk of intrafractional movement and maximizes on linear accelerator capacity.

Clinical Studies

Early-stage NSCLC

In 2010, Videtic et al.[38] published clinical outcome data of medically inoperable stage I NSCLC patients treated with IMRT-based SABR. In this case series, 26 patients received 50 Gy in 10 fractions, delivered with seven nonopposing, noncoplanar-intensity modulated beams. The median heterogeneity index was 1.08 (range, 1.04–1.2). Seventy-one patients had histological confirmation and 89% of tumors were in a peripheral location (median size 2.2 cm). The treatment was well tolerated, with only one patient (who was on oxygen before commencement of treatment) experiencing grade 3 dyspnoea. Overall, there was no significant change in pulmonary function tests post-treatment and no treatment-related deaths. Three-year local control was comparable to surgical series and 3DCRT-based SABR series at 94.4%, and 3-year OS was 52%.

Looking further into toxicity of IMRT for stage I NSCLC, Palma et al.[39] compared radiological and clinical patterns of treatment-related pneumonitis (TRP) in patients who received SABR delivered either with VMAT (a rotational form of IMRT using up to 5 arcs) or 3DCRT (8–12 noncoplanar static beams). Seventy-five patients (25 VMAT, 50 3DCRT) were included in the study. Patients between the two arms were matched demographically, for dose, fractionation, PTV size (<100 cc), and tumor location. Interestingly, although 57% patients developed radiological changes in the lung, only 5% developed clinical symptoms. The toxicity profile is similar to that of 3DCRT-based SABR. There was no statistically significant difference between the groups in terms of the rate of clinical TRP.

Ong et al.[13] compared VMAT, IMRT, 3DCRT, and dynamic conformal arc techniques for SABR of stage I NSCLC. Although all met the normal tissue dose constraints,

TABLE 1. Advantages and Disadvantages of IMRT for Lung Cancer

Advantages	Disadvantages
Ability to spare organs at risk	Increased contouring, planning, and quality assurance time
Better coverage of irregular shaped targets	Increased need to accurately delineate clinical target volumes and involved nodes requiring treatment
Ability to dose escalate	Need for image guidance
Able to treat synchronous primary tumors and multiple targets simultaneously	Sharp dose gradient—may lead to under-treatment of micrometastatic disease
Enables treatment of larger radiotherapy volumes to radical dose	Potential interplay effects depending on fractionation and complexity of IMRT technique used
	Need for rigorous quality assurance programme
	Low-dose radiotherapy bath

IMRT, intensity-modulated radiotherapy.

IMRT was useful in further shaping the beam around critical organs at risk e.g., chest wall and VMAT had an advantage over other techniques in terms of dose conformity and treatment time. A further paper by the same group reported on a retrospective series of 18 patients with large volume (median PTV 137 cm^3), stages I–II lung tumors without nodal metastases treated with VMAT.[40] A risk-adapted fractionation scheme of either five fractions of 11 Gy or eight fractions of 7.5 Gy was used with the following planning objectives: 95% of the PTV should receive at least the nominal fraction dose, 99% of the target volume should receive greater than or equal to 90% of the prescription dose, and the maximum PTV dose was between 110% and 140% of the prescription dose. Five patients developed grade of greater than or equal to 2 radiation pneumonitis (three with grade 2 and two with grade 3), all cases occurred in plans without a high priority optimization objective on contralateral lung. They demonstrated that acute TRP was best predicted by contralateral lung V5 ($p < 0.0001$).

Locally advanced NSCLC

Prospective studies. A potential advantage of IMRT over 3DCRT is the ability to safely escalate radiotherapy dose. One of the first studies to address this issue was a phase I dose escalation study (84 Gy/35 fractions) of IMRT in stage III NSCLC and induction chemotherapy.[41] This study was halted after the enrolment of five patients as one patient died of pneumonitis. This may have been due to an adverse effect of chemotherapy on baseline lung function or the hypofractionated dose regime; however, this study has been criticized for using an inadequate dose calculation algorithm, leading to systematic underestimation of doses to the tumor and organs at risk.[42]

It was widely anticipated that RTOG 0617, a prospective, randomized phase III trial comparing 60 Gy/30 daily fractions with 74 Gy/37 daily fractions (concurrently with paclitaxel/carboplatin), with or without cetuximab would be the first phase III trial to confirm the benefit of dose escalation beyond 60 Gy in stage III NSCLC.[7] Surprisingly, at interim analysis the data suggested a survival disadvantage for the high-dose arm as well as inferior local control rates, indicating that dose escalation using conventional fractionation (resulting in increased overall treatment time) is not the ideal approach for NSCLC. The reasons for this are the subject of some debate, but possible explanations include: increased heart dose, extended therapy duration, underreported grade 5 events, compromised target coverage, or likely a combination of these factors. It should be noted that just under half of the patients in this study were treated with IMRT (46.5%). Although patients were stratified by treatment delivery technique and the proportions of patients treated with IMRT were balanced between treatment groups (46.1% in 60 Gy arms and 47.1% in 74 Gy arms), the delivery of 74 Gy was probably challenging, particularly in patients treated without IMRT, given the gross tumor volume (GTV) (mean 124.7 in 60 Gy arms and 128.5 cc in 74 Gy arms). A subsequent analysis on patient reported outcome demonstrated a significantly worse quality of life on the 74 Gy arms at 3 months after treatment.[43] Interestingly, the decline in quality of life was significantly reduced with the use of IMRT compared to 3DCRT suggesting that the use of improved radiotherapy treatment techniques may be beneficial.

More recently, results of a phase I trial of hypofractionated, dose escalating IMRT in NSCLC were published.[44] Seventy-nine patients received dose escalated treatments based on the patients' stratified risk for TRP in 25 daily fractions. Patients with all stages of disease were recruited and 62% received chemotherapy in the neoadjuvant or adjuvant setting. Patients were all positron emission tomography staged, planned using four-dimensional (4D) CT and the treatment was delivered with helical tomotherapy. The dose was prescribed such that 95% of the PTV volume received the prescription dose. Despite escalation to doses of up to 85.5 Gy/25 fractions, no grade 3 acute or late esophageal toxicity and no grade 3 pneumonitis was seen; however, six grade 4/5 toxicities were encountered in the form of massive hemoptysis and bronchocavitary fistula. Both these toxicities were associated with centrally based tumors, doses above 75 Gy, and specific 1–3 cc doses to the proximal bronchial tree. No constraints for proximal bronchial tree were specified in the trial protocol. After a median follow-up of 17 months median survival was 16 months and 3-year OS was 29%, which does not appear superior to historical outcome.

Retrospective studies. The largest body of evidence for IMRT in locally advanced NSCLC originates from three retrospective publications of patient cohorts from the same cancer center (MD

TABLE 2. Planning Studies Comparing IMRT to 3DCRT

Publication	No. Patients	DiagnosesPTV Size (ccm)Prescription	3DCRT Technique	IMRT Technique	PTV	Both Lungs	Contralateral Lung	Ipsilateral Lung	Heart	Spinal Cord
Cattaneo, 2008[9]	13	Stage III NSCLC394 (215–745)34–39x1.8 Gy	3–5 fields	Tomotherapy, 2.5 cm jaw width, modulation factor <3	IMRT (V95%)	IMRT (mean, V15, V20, V30, V40)	–	–	IMRT (mean, V45, V50, V60)	NS
Chan, 2011[10]	24	Stage III NSCLC–30x2 Gy	5–7 coplanar fields	VMAT: 2 204° arcs.Hybrid-VMAT: 2 204° arcs and 2 static fields	IMRT (CI, (D5%–D95%))	IMRT (mean, V20, V10)3DCRT (V5)	–	–	IMRT (V40)	IMRT (max)
Christian, 2007[30]	10	Stages IB–IIB NSCLC197 (103–272)32 x 2 Gy	6 noncoplanar fields	3–9 coplanar fields6 noncoplanar fields	IMRT(PTV_{90}/V_{20lung})	IMRT(PTV_{90}/V_{20lung})	–	–	–	IMRT (max)
De Bree, 2012[8]	20	Inoperable NSCLC838 (407–1574)30–33x2 Gy	5 fields	VMAT, 2 arcsStatic field IMRT, 7 coplanar fields	IMRT (CI)	IMRT (mean)3DCRT (V5, V20)	–	–	IMRT (V40)	IMRT (max)
Liu, 2004[11]	10	Stages I–IIIB NSCLC403 (65–762)35x1.8 Gy	4 fields: AP/PA fields and oblique off-cord fields	SW-IMRT plans, 3–9 coplanar fields	IMRT (CI)	IMRT (V20, V30, mean)3DCRT (V5)	–	–	–	–
McGrath, 2010[29]	21	Stage IA NSCLC57 (22–125)4x12 Gy	7–10 nonopposing noncoplanar fields	1 partial arc of 180°	NS	IMRT (20 Gy, 12.5 Gy, 10 Gy, 5 Gy)	–	–	NS	NS
Murshed, 2004[12]	41	Advanced stage NSCLC—	9 equidistant coplanar 6 MV fields	SW-IMRT, 9 equidistant, coplanar fields	IMRT (CI), 3DCRT (HI)	IMRT (V10, V20)	NS	NS	IMRT (V40)	3D (max)
Ong, 2010[13]	18	Stage I NSCLC34 (3–67)8x7.5 Gy –3x 18 Gy	10 noncoplanar fields	VMAT, 2 arcs	IMRT (CI)	3DCRT (V20)	3DCRT (V5)	–	–	IMRT (max)
Simeonova, 2012[14]	20	Stages I–IV NSCLC515 (CTV)–	3–6 18 MV fields	13 coplanar fields17 noncoplanar	IMRT (min)	–	IMRT (mean, D30%)	IMRT (D30%, V20)	NS	IMRT (max)
Zhang, 2011[31]	15	Early stage LC6 (17–161)5x10 Gy	9–11 noncoplanar fields	Coplanar VMAT Noncoplanar VMATFFF VMAT	IMRT (CI, GI)	IMRT (mean, V5, V20)	–	–	–	–

3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; VMAT, volumetric modulated arc therapy; CI, conformity index; GI, gradient index; HI, homogeneity index; Vx, volume receiving x Gy; max, maximum dose; Dx%, dose to x% of the organ; –, no information in the publication; NS, no significant difference.

TABLE 3. Planning Studies Comparing Different Types of IMRT Technique

Publication	No. Patients	DiagnosisPTV Size (ccm)Prescription	IMRT Technique	PTV	Both Lungs	Contralateral Lung	Ipsilateral Lung	Heart	Spinal Cord	Treatment Time
Bertelsen, 2012[32]	15	NSCLC252 (77–509) 33 x 2Gy	SS-IMRT 7–9 fields Single arc VMAT	NS	VMAT (V20)	–	–	–	–	VMAT
Chan, 2011[10]	24	Stage III NSCLC-30x2 Gy	VMAT: 2 204° arcs. Hybrid-VMAT: 2 204° arcs and 2 static fields	Hybrid-VMAT (D5%–D95%)	Hybrid-VMAT (mean, V20, V10, V5)	–	–	VMAT (V40)	NS	VMAT
Holt, 2011[33]	27	Early-stage LC45 (14–102)3x18Gy	Noncoplanar IMRT (NC-IMRT) Coplanar VMAT	NC-IMRT	VMAT & NC-IMRT (mean, V5, V20)	–	–	VMAT (max)	NCP-IMRT (max)	VMAT
Jiang, 2011[34]	12	Locally advanced NSCLC34x2Gy	SS-IMRT: 5–7 beams VMAT (1 full arc) P-VMAT (200° partial arc)	VMAT (CI, HI)	IMRT (V5, V10)VMAT & P-VMAT(V30, V20, mean)	IMRT (V5, V10) P-VMAT (V30, V20, mean)	NS	NS	NS	P-VMAT
Ong, 2010[13]	9	Stage I NSCLC34 (3–67)8x7.5G –3x 18Gy	VMAT, 2 arcs 9–10 coplanar FF-IMRT fields	VMAT (CI)	NS	NS	–	–	–	VMAT
Simeonova, 2012[14]	20	Stages I–IV NSCLC515 (CTV)-	13 coplanar FF-IMRT fields17 noncoplanar FF IMRT fields	NS	–	17F-IMRT (mean, D30%)	NS	NS	NS	13F-IMRT
Weyh, 2012[35]	8	Stages I + II NSCLC–4 x 12 Gy	Helical tomotherapy (HT)FF-IMRT VMAT	HT (CI)	NS	–	–	NS	NS	VMAT
Zhang, 2011[31]	15	Early stage LC6 (17–161)5x10 Gy	Coplanar VMAT Noncoplanar VMATFFF VMAT	FFF VMAT (mean target dose)	NS	–	–	–	–	–

IMRT, intensity-modulated radiotherapy; PTV, planning target volume; CI, conformity index; GI, gradient index; HI, homogeneity index; Vx: volume receiving x Gy; max, maximum dose; Dx%, dose to x% of the organ; VMAT, volumetric modulated arc therapy; SS_IMRT, step and shoot IMRT; FFF, flattening filter free; –, no information in the publication; NS, no significant difference

Anderson Cancer Centre, Texas). It should be emphasized that as the treatment groups were not fully balanced and positron emission tomography staging was introduced at the time of recruitment to the IMRT cohorts, the data need to be interpreted with caution. Nevertheless, these studies all suggested improved outcomes with IMRT, reporting less toxicity and a superior OS.

Yom et al.[45] evaluated the rate of TRP in 68 NSCLC patients (85% stage III) treated with IMRT between 2002 and 2005, and compared this to a group of 222 historical controls treated with 3DCRT (2000–2003). Reasons for implementing IMRT included large treatment volume, failure to meet normal tissue dose constraints for 3DCRT, synchronous lung primary tumors, and poor baseline pulmonary function. In both groups, the majority of patients received a treatment dose of 63 Gy in 35 fractions and concurrent platinum-based doublet chemotherapy. Despite a larger GTV in the IMRT group (194 versus 142 cc), patients achieved significantly lower volumes of lung receiving 20 Gy (V20), however had larger volumes of lung receiving 5 Gy (V5) compared to the 3DCRT group. With a median follow-up of eight (0–27) and nine (0–56) months, respectively, the incidence of greater than grade 3 TRP was significantly lower in the IMRT group than in those treated with 3DCRT (8% versus 22% at 6 months). Local control in the IMRT group at 12 months was 55.3% with an estimated OS at 12 months of 57%.

Liao et al.[46] examined the effect of IMRT, accounting for motion (4DCT), on toxicity and clinical outcome in locally advanced NSCLC. Ninety-one patients (some of whom were also included in the Yom study) were treated with 4DCT/IMRT between 2004 and 2006. These were compared to 318 patients receiving 3DCRT between 1999 and 2004. Both groups received a median dose of 63 Gy using conventional fractionation. The IMRT group contained a greater proportion of patients who were older, current smokers, or staged with positron emission tomography CT (82% 4DCT IMRT versus 49% 3DCTRT). GTV was not reported. Again, this study confirmed a reduced rate of TRP in the IMRT group, with significantly lower V20 percentages (34% versus 37%), at the expense of a higher V5 (65% versus 57%). The authors reported similar rates of local control and distant metastases, but an improvement in OS in the IMRT group (median survival times 1.40 years for the 4DCT/IMRT group and 0.85 year for the 3DCRT group).

Their most recent study assessed long-term clinical outcome of patients treated with 4DCT IMRT (n = 165; 76% stage III) with or without concurrent chemotherapy. The median radiation dose was 66 Gy given in 33 fractions[47] and median GTV was 124.6 cc (range, 4.3–730 cc). Eleven percent of patients developed greater than or equal to grade 3 TRP at 6 months and one patient was affected by grade 3 pulmonary fibrosis at 18 months. The majority of the 29 patients (18%), who experienced grade 3 esophagitis settled within 6 weeks, however four went on to develop an esophageal stricture requiring further intervention. Overall, the incidence and severity of toxicities were lower in IMRT patients than historical control cohorts who received 3DCRT. With a median 16.5 months follow-up, 2-year disease free and OS were 38% and 46%, respectively.

Other centers have also published encouraging retrospective outcome data for IMRT in locally advanced NSCLC. Memorial Sloan Kettering assessed the toxicity of IMRT in 55 stages Ib–IIIb (62% stage III) NSCLC patients between 2001 and 2005.[48] Patients received a dose of 60 Gy in 30 fractions with either sequential (53%) or concurrent (24%) chemotherapy, unless contraindicated. Mean GTV was 136 cc. With a median follow-up of 12 months, six (11%) patients reported grade 3 pulmonary toxicity, and two (4%) developed grade 3 esophageal toxicity. Two-year OS was 58% with a median survival of 25 months. Govaert et al.[49] experienced similar findings in 71 stages IIb–IIIb NSCLC patients treated with IMRT between 2008 and 2011. Patients received up to a dose of 66 Gy in 33 fractions with chemotherapy. Mean GTV volume was not reported. No grade 3/4 pulmonary or esophageal toxicity was observed, and there were no treatment-related deaths. After median follow-up of 12 months, median survival was 29.7 months, which translated to a 56% two-year OS. A group at the Netherlands Cancer Institute assessed at the rate of acute[50] and late[51] toxicity following hypofractionated IMRT (66 Gy in 24 fractions) and concurrent chemotherapy for NSCLC in two separate papers. Thirty-five percent of patients developed any greater than grade 3 acute toxicity and 7% patients developed TRP. Six percent (11/171) developed severe late esophageal toxicity in the form of stenosis (8/11) or fistula (3/11), which was comparable to historical cohorts treated with 3DCRT. Two-year OS was 52%.

Population-based studies. Shirvani et al.[52] investigated predictors of IMRT use in the United States between 2001 and 2007, using the Surveillance, Epidemiology, and End Results (SEER) Medicare database. They reported that the year of diagnosis and treatment in a dedicated radiotherapy center were the only independent predictors of IMRT use. Lung and esophageal toxicity was equal between the IMRT and 3DCRT groups. A further population-based study using the SEER database compared treatment outcomes in stage III NSCLC for IMRT, 3DCRT, and two-dimensional radiotherapy (2DRT) planning techniques.[53] This study was conducted to address fears that IMRT may cause inaccuracies in dose and increased long-term toxicity, which in turn could affect survival. This analysis of nearly 7000 patients confirmed that IMRT was associated with similar toxicities and OS to 3DCRT, with both techniques showing an advantage over 2DRT.

Challenges in implementing IMRT

Although the majority of planning studies and limited clinical data support the use of IMRT in lung cancer, implementation comes with clinical and technical challenges. IMRT is a more complex technique than conventional 3DCRT[23] and places higher demands on treatment planning, dose calculation algorithms, and delivery systems. As IMRT relies on computerized inverse planning, additional organs at risk such as the heart, brachial plexus, central airways, and esophagus need to be contoured to instruct the system to avoid depositing high dose in these tissues. This is time consuming for the clinician and the treatment planner.[54,55]

Dose calculation in lung tissue requires the use of a model-based calculation algorithm (type B), as use of measurement-based algorithms (type A) give rise to inaccurate scatter modeling in lung tissue and deviations of up to 5% between calculated and measured doses.[56–58] Discrepancies between type A algorithms and measurements are larger for IMRT compared to 3DCRT[59] and so the use of type B algorithms is a prerequisite when planning IMRT for lung patients. The increased complexity of IMRT plans also require additional quality assurance tests to be routinely performed on the delivery system (and commonly across Europe, on individual patient plans).[60–62]

Breathing motion, especially in lung cancer, influences the dose delivered to the patient. This variation with respiration creates two organ motion effects: the gradient/blurring effect and the interplay effect. The gradient effect occurs as the tumor moves, "blurring" the area in which the tumor is in. This effect can be compensated for by radiating the whole envelope of motion (within an internal target volume),[63,64] by calculating a margin based on the probability distributions of the cumulative dose[65] or by a tracking or gating technique.[66,67] The interplay effect is caused by the lack of synchrony between the moving aperture (e.g., MLC) and tumor motion. There is concern that the highly conformal fields, numerous MLC positions required for IMRT and intra-fractional tumor motion may lead to target miss. Several authors have evaluated the interplay effect for conventional fractionated IMRT treatments using sinusoidal motion[34,68–73] as well as realistic patient motion.[66–68] All reported that the interplay effect could alter the dose distribution of a single fraction, but not a fractionated course of treatment. Jiang et al.[34] demonstrated a maximum dose variation of 30% for one field in one fraction, 18% for all five fields after one fraction, and less than 1–2% after 30 fractions. Even with SABR there is a negligible interplay effect as effects average out due to the larger number of monitor units and increased treatment time required.[74–76] However, interplay may cause an effect for extreme hypofractionation/SABR combined with very complex IMRT/VMAT deliveries. Strategies to reduce the interplay effect include increasing the number of arcs,[74] decreasing the dose rate and therefore prolonging the treatment time[34] or avoiding an MLC motion perpendicular to the tumor motion.[74]

In comparison to 3DCRT, IMRT increases the low-dose bath to the patient as a greater number of beams and monitor units are used (an increase in monitor units is necessary to compensate for large parts of the fields being blocked by MLCs and this increases head leakage and scatter radiation). There are concerns that this low-dose bath may increase the risk of acute and late pulmonary toxicity, as well as the risk of second malignancy.[11,21,23,77] The potential survival benefit of IMRT outweighs the secondary cancer risk in NSCLC, however toxicity is of importance. A correlation between low doses to the lung and fatal pneumonitis has been demonstrated in mesothelioma, leading to recommended threshold doses of

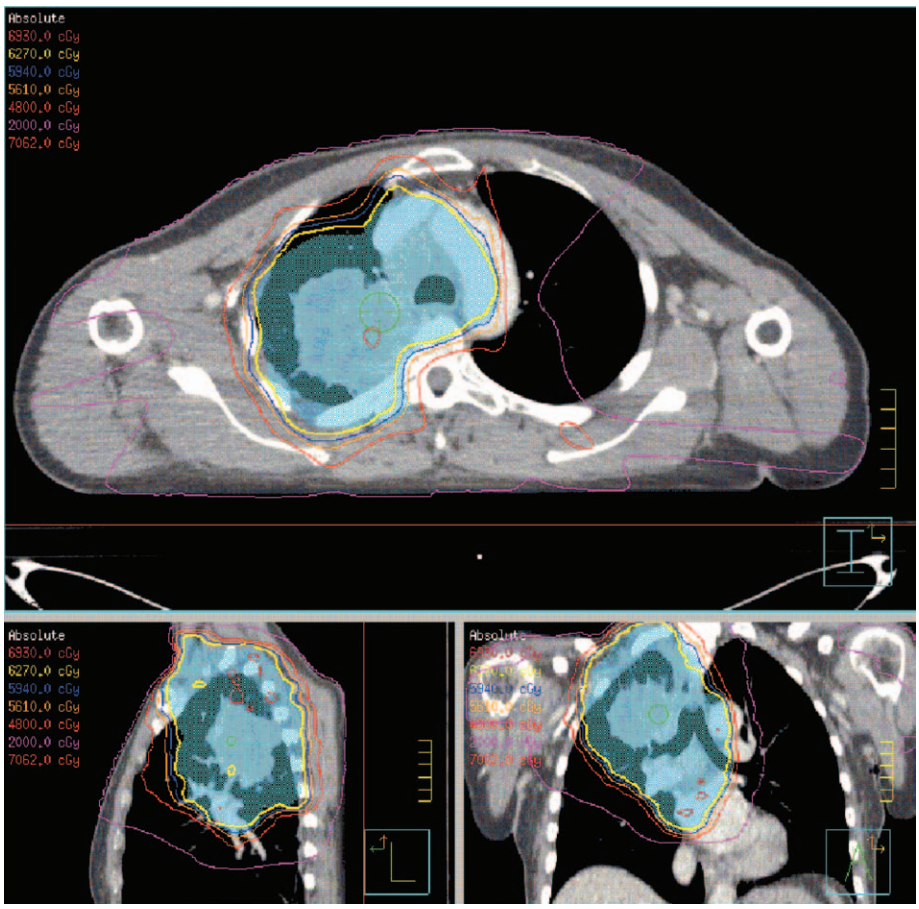

FIGURE 1. Patient with large volume disease (T3N3M0) treated with seven fields fixed-beam step and shoot IMRT. 66 Gy in 33 fractions prescribed to PTV_IMRT (PTV edited from the skin by a 0.5 cm isotropic 3D margin and from the spinal canal by a 1.0 cm isotropic 3D margin). Mean lung dose 19.9 Gy, V20 34.5%, maximum spinal cord 48.9 Gy. PTV, planning target volume; V20, percent volume of total lung receiving 20 Gy; IMRT, intensity-modulated radiotherapy; 3D, three dimensional.

TABLE 4. Examples of Ongoing Clinical Trials Utilizing IMRT for Dose Escalation

Trials Evaluating Personalized Dose Escalation Based on Dose Delivered to OARs	Trials Evaluating an Increased Dose to Selected Parts Within the Tumor, Defined by Functional Imaging (Dose Painting)
Isotoxic IMRT (NCT01836692)	**PET boost (NCT01024829)**
Prospective multicenter single arm feasibility study	Randomized multicenter phase II study
Stage III NSCLC	T2-4, N0-3, M0 inoperable, NSCLC
Sequential chemoradiotherapy	RT alone, sequential, or concurrent chemoradiotherapy
Hyperfractionated, accelerated, and dose-escalated radiotherapy with IMRT and image guidance. Dose based on prespecified normal tissue doses	66 Gy given in 24 fractions of 2.75 Gy delivered with IMRT +/- integrated boost to whole tumor, or the FDG PET-CT 50% SUV_{max} area of the primary individualized to meditational organs at risk (with or without chemotherapy)
Maximum dose 79.4 Gy in 39 twice-daily (BD) fractionsPrimary outcome: delivery of isotoxic IMRT to dose >60 Gy EQD2 (total biologically equivalent in 2 Gy fraction)Proceed to phase II if dose escalation possible in >80% patients	Primary outcome: local progression-free survival at 1 yearThe planning results of the first 20 patients have been published. It was possible to dose escalate 75% of patients to 72Gy, with dose-limiting organs being the mediastinal structures and the brachial plexus[80]
Maastro study (NCT01166204)	**RTOG (NCT01507428)**
Nonrandomized monocenter phase II study	Randomized multicenter phase II study
Stages I–III NSCLC	Stage III NSCLC
Concurrent chemoradiotherapy	Concurrent chemoradiotherapy
Radiotherapy delivered with IMRT to an individualized mean lung dose of 20 Gy +/-1	60 Gy in 30 daily fractions delivered with IMRT +/- adaptive radiotherapy based on FDG-PET/CT scan between fractions 18 and 19
45Gy/30 BD fractions for first 3 weeks followed by once daily fractions of 2 Gy until the target dose has been reached	Max dose 80.4 Gy in 30 daily fractions, individualized to mean lung dose 20 Gy
Primary outcome: overall survival	Primary outcome: local progression-free survival

IMRT, intensity-modulated radiotherapy.

mean lung dose of less than 8.5–13 Gy, V5 less than 60–75%, and V10 less than 50%.[20,78,79] However, a clear relationship between V5 lung doses and severe pulmonary toxicity for IMRT in NSCLC is lacking and as yet there is no consensus as to suitable threshold doses.

DISCUSSION AND FUTURE DIRECTIONS

By facilitating improved beam shaping around complex structures, IMRT offers the potential to optimize dose delivery to a target volume while sparing surrounding normal tissue. This increases the scope to safely escalate the dose, boost subvolumes, and treat larger radiotherapy volumes in the radical setting than was previously possible with 3DCRT (Fig. 1).

The key clinical question regarding this technique is whether IMRT can lead to an improvement in OS as a result of reduced toxicity and/or isotoxic dose escalation (individualized dose escalation based on predefined safe organs at risk dose constraints) leading to improved local tumor control. Patients with a high burden of disease may relapse both locally and distantly, making outcomes similar whether or not the dose to the primary has been optimized. Robust, randomized evidence demonstrating improved clinical outcomes with IMRT is lacking, and concerns regarding the need for extra resources in terms of treatment planning, delivery time, and financial cost may go some way to explain why the uptake of this technique remains low.[15]

There is little doubt from planning studies that there is a dosimetric advantage of using IMRT for lung cancer, which should justify the increase in time requirements for contouring, planning, and treatment verification. A specific concern about the use of IMRT for lung is the amount of tumor motion during treatment seen in this site compared to, for example, head and neck cancers. This can be partly remedied with 4DCT and advanced planning techniques, and encouragingly the interplay effect does not seem to cause any clinical detriment.

We would argue that the clinical evidence reviewed in this article demonstrate that IMRT can be delivered safely with acceptable acute and late toxicities. IMRT facilitates lowering of critical dosimetric parameters such as V20, and although lower doses of radiation are delivered to more tissue, concerns that this "low-dose bath" may adversely affect long-term lung function or increase second malignancy risk have not been reported in prospective studies. Crucially retrospective studies report disease-free and OS figures which seem to show an advantage over those achieved with conventional 3DCRT. As these studies were not randomized, there is a likelihood of inherent bias. The IMRT cohorts will have been treated more recently meaning that stage migration may play a part in the improved survival as well as improved patient setup imaging such as Cone Beam CT. Conversely, as IMRT was initially often used for patients unable to meet 3DCRT dose constraints, this group may also contain a higher risk population that would have been expected to have a lower survival.

The outcome of the recent RTOG 0617 study showing no benefit for the higher dose arm has left some questioning efforts to dose escalate in lung cancer radiotherapy. Although on face value it would seem that the "dose escalation in lung cancer" debate has stalled, we need to be cautious not to dismiss "radiotherapy treatment intensification" as a concept. There are many unanswered questions surrounding RTOG 0617 regarding dose delivery and radiotherapy quality assurance and it is important to acknowledge that less than 50% patients in this trial were treated with IMRT. In addition, there

TABLE 5. Minimum Requirements for Safe Delivery of IMRT

Minimum Requirements for the Safe Delivery of IMRT
4D CT planning scan or equivalent
Delineation of additional organs at risk for inverse dose plan computation
Type B algorithm for dose calculation
Cone beam CT verification
End-to-end testing using a anthropomorphic or semianthropomorphic phantom before first clinical use
Risk assessment of interplay effects from the IMRT technique and fractionation employed
Dedicated machine IMRT QA program
Patient-specific IMRT QA program including independent MU verification (calculation or measurement based)
Patient-specific QA of transfer of the treatment plan to the treatment machine

IMRT, intensity-modulated radiotherapy; QA, quality assurance; MU, monitor unit.

remains good evidence to show that improved local control can improve survival. There is therefore a general consensus that radiotherapy treatment intensification with advanced radiotherapy techniques and image guidance still represents a valuable opportunity to improve outcomes for lung cancer patients. The situation however is complex, with consideration for different fractionation regimes and perhaps a move to greater individualization of treatment. To this end a number of clinical trials to address these issues are open or in set up; examples of these are presented in Table 4.

In conclusion, from the current evidence available, IMRT can achieve better dose conformality, avoid organs at risk and lower treatment toxicity. However, compared to conventional 3D techniques, the planning process and treatment delivery is time consuming and places strain on valuable resources. Our recommendations for the minimum requirements to deliver IMRT safely are presented in Table 5. Further prospective data are needed to strengthen the evidence base for this technique. It is hoped that eventually we may be able to correlate clinical features of the tumor and radiotherapy planning parameters with toxicity and survival. At present IMRT is best indicated when the tumor volume is near to an organ at risk or when treatment volumes are too large to treat to a radical dose with 3DCRT. However, research activity into dose escalation for lung cancer is intensifying and once the optimal approach to this is established, IMRT will undoubtedly play an essential role in radiotherapy treatment delivery.

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